This is a summary of a Cochrane Review. The full citation and the names of the researchers who conducted the Review are listed in the References section below

Cochrane Review Summary for Cancer Nursing: Drug Therapy for Cancer-related Fatigue

Background

Cancer-related fatigue (CRF) is one of the most debilitating symptoms in patients with cancer. It is prevalent at the time of diagnosis, during and after antineoplastic treatment, and in patients with advanced disease. The multi-factorial and complex nature of CRF makes it challenging for health professionals to identify a clear underlying mechanism and manage this symptom effectively. Often, the management plan for CRF (whether pharmacological or non-pharmacological) can be further complicated by the co-existence of other symptoms. This systematic review (1) is therefore important in informing health professionals on the effectiveness of pharmacological management for CRF.

Objective/s

The objectives of this review were to (i) assess the effectiveness and adverse events associated with drugs used for CRF in patients with cancer, compared with standard care or non-pharmacological interventions and (ii) to determine optimal dose and duration of drug therapy(ies). Only randomised controlled trials (RCTs) were included in this review.

Intervention/Methods

The Cochrane review included 31 RCTs. In total, 7104 participants older than 18 years were included in the review. Patients included in these trials were at different point of the cancer treatment spectrum. All included trials compared a drug therapy with placebo, standard care or an alternative non-pharmacological treatment for CRF. All included trials included differences in fatigue between intervention group and controls as the outcomes of interest, using patient self-reported measures or other validated research instruments. The methodological soundness varied across all included trials. The trials assessed the effectiveness of four classes of drugs for improving CRF; psychostimulants, haemopoietic growth factors, anti-depressants and progestational steroids.

Results

Psychostimulants

Data from a meta-analysis of five studies (N=410) showed that, overall, psychostimulants (methylphenidate and dexamphetamine) had statistically significant effects in reducing CRF compared to placebo. The overall effect Z score=2.83 (p=0.005, Standard Mean Difference [SMD]=-0.28, 95% Confidence Intervals [CI]: -0.48 to -0.09), with I^2 statistics of 0%, indicating no

important heterogeneity between the trials. The dosages of methylphenidate used the four included trials varied (from 5mg up to 20mg every 24 hours).

Haemopoietic growth factors
In this review, the effects of two haemopoietic growth factors (erythropoietin and darbopoietin) were analysed separately. Data from a meta-analysis of 11 studies (N=2348) showed that, overall, erythropoietin had statistically significant effects in reducing CRF compared to no intervention. All these trials recruited anaemic cancer patients with a Haemoglobin level <12g/dl). The overall effect Z score=7.31 (p<0.00001, SMD=-0.36, 95% CI: -0.46 to -0.26), with an I^2 statistics of 20%. The heterogeneity was probably due to study quality and lack of blinding in allocation in some of the included trials. For darbopoietin, data from a meta-analysis of four studies (N=964) showed that, overall, darbopoietin had a small but statistically significant effect in reducing CRF compared to no intervention. The overall effect Z score=1.96 (p=0.05, SMD=-0.13, 95%CI: -0.27 to 0.00), with I^2 statistics of 0%, indicating no important heterogeneity between the trials.

Anti-depressants
Two trials assessed the effects of paroxetine in reducing CRF. Data from the meta-analysis of the two trials (n=643) showed that, overall, paroxetine was not superior to placebo in reducing CRF (p=0.29).

Progestational steroids
Four trials assessed the effects of mesgestrol acetate or medroxyprogesterone acetate. Data from the meta-analysis of the four trials (n=587) indicated no difference between progestational steroids and placebo for reducing CRF. There was significant heterogeneity between the trials (I^2=98%).

Adverse effects
The majority of trials included in this review had minimal reported adverse events compared to the control/placebo groups for all four classes of drugs. The review did not report on the specific types of adverse events.

Conclusions
There is now evidence of some benefits in using methylphenidate for treating CRF compared to placebo. Although haemopoietic growth factors had significant effects in treating fatigue in anaemic cancer patients compared to no intervention, and minimal adverse events were reported it should be noted that evidence from another systematic review (2) suggests there are safety concerns and side effects associated with these drugs. Anti-depressants and progestational steroids were not superior to placebo.

Implications for Practice
- For patients with CRF, the review author recommended that methylphenidate may be considered for use in a dose of 10 to 20mg per day depending on response. There were minimal serious adverse

effects, however, contra-indications to this drug should be considered before use.

- Erythropoietin and darbopoietin can no longer be recommended for treating CRF due the adverse events associated with these drugs.

Reference

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2. Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, Zwahlen M, Clarke M, Weingart O, Kluge S, Piper M, Rades D, Steensma DP, Djulbegovic B, Fey MF, Ray-Coquard I, Machtay M, Moebus V, Thomas G, Untch M, Schumacher M, Egger M, Engert A. Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials. *Lancet*.2009;373:1532-1542.

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